# 15 Global Regulatory Strategy

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## Introduction

The ultimate goal of a regulatory strategy is to enable patient access, and it is within this context that a regulatory professional must provide a regulatory strategy. A regulatory strategy can be defined as a science-driven assessment of a product's development options, key considerations and likely regulatory outcome. It should span the earliest development stages through further modifications planned postauthorization. It should encompass key milestones and decision points; consider regulatory objectives, hurdles, the regulatory landscape and precedents; and characterize risks to potential success in delivering a specific regulatory outcome. This regulatory outcome, in turn, will have broader consideration because it will link to the potential for patient access, commercial acceptability and uptake and, therefore, likely business outcomes.

A global regulatory strategy should combine regulatory requirements and business objectives. It often is defined by a global regulatory expert, who must consult with a cross-functional team. The cross-functional team should comprise experts who: provide regional regulatory requirements and regulatory intelligence on expectations, precedents and competition; correspond with local regulatory authorities; enable document management and submission processes; and provide specific functional expertise such as labeling, CMC, nonclinical and clinical. There also are internal and external business considerations that can drive a specific global regulatory strategy's development. Examples of considerations that influence global strategy are the organization's financial situation or the product's intellectual property status. External examples include the organization's business partner or investor community viewpoints.

Global regulatory organizations must provide comprehensive development plan input throughout the product's lifecycle. This input starts in the preclinical development phase and continues through postmarketing. Functional regulatory units provide input on the likely acceptability of the planned evidence package that will be generated for the regulator and subsequent stakeholders, specific regulatory requirements for product development, postmarketing, regulatory submission management, regulatory intelligence, product labeling and advertising and promotion.

### *Interdisciplinary Factors and Alignment*

A global regulatory strategy cannot be planned in isolation from other factors contributing to an innovative new product's overall success. The most successful new products use a multi-pronged development program approach, addressing business, scientific and regulatory outcomes. The integrated multidisciplinary product development concept is shown in **Figure 15-1**.

### *Business Strategy*

Business outcomes are defined broadly as those accomplishments driving business results, including revenue, earnings, cash flow, return on capital and valuation.

**Figure 15-1. Multidisciplinary Product Development**


Regulatory decisions can affect the time-to-market, label claims and reimbursement directly and, consequently, a new product's sales, profitability and contribution to business results. Therefore, it is critical regulatory professionals understand the organization's business strategy to plan the product development and postauthorization activities within this framework and as members of a multidisciplinary global team planning an integrated product strategy.

Early sponsor development of a Target Product Profile (sponsor TPP) by the multidisciplinary team establishes key product attributes and provides an opportunity to consider financial factors and build a sophisticated financial model to develop anticipated business outcomes. It also will assist in determining the break-even point at which no further development should be undertaken, as the business outcomes will not be positive, and product divestiture may be considered. Ultimately, companies should seek improved patient outcomes compared to existing therapies and, if these are positive, it is likely the product also may provide financial return.

Note, a sponsor TPP should be differentiated from a formal regulatory TPP prepared in accordance with FDA guidance[1] and serving as a format for sponsor discussions with the regulatory authority. The relationship between the two types of product profiles is important, as a sponsor TPP will guide the formal TPP and development plan, contributing to overall business objectives.

A sponsor TPP may include optimal and acceptable label claims compared to currently available products and competitors in development. Similarly, it may articulate an acceptable safety profile and risk-benefit analysis, as well as

planned product presentation. The sponsor TPP will establish the global development plan framework, incorporating data and regulatory requirements and strategies to gain marketing approval in the shortest possible timeframe. Ultimately, the company may ask a regulatory professional the likelihood of achieving the product's targeted labeling claims and when it will be achieved.

Increasingly, the overall goal is a global development program with simultaneous, multimarket submissions and approvals. However, many factors can influence the need for prioritizing an individual country or region, identifying opportunities to enable early or more cost-effective market entry. For example, orphan drug programs vary significantly. Some are limited to a reduction in regulatory agency fees, while others, like the US, have more generous programs that include additional agency support and development grants. A second important example is FDA's accelerated approval program that provides an opportunity to gain early approval based on surrogate or intermediate endpoints, thus reducing premarket development costs and time, and leading to early market entry.

Similar programs to support innovative new medicines are available in Europe, including accelerated assessment of medicines of major public health interest via the Centralised Procedure, especially ones that are therapeutic innovations. Accelerated assessment usually takes 150 evaluation days, rather than the standard 210 days. In addition, in 2016, a program to enable accelerated assessment of PRIority MEdicines (referred to as PRIME) was introduced. PRIME eligibility criteria are similar to those for accelerated assessment but result in additional dialogue, support and connectivity within the EU regulatory network. It is intended for medicines in development to address an unmet medical need. There also are mechanisms in some jurisdictions to allow approval based on more limited data (e.g., Phase 2 studies or surrogate endpoints) due to the new medicine's promising nature. The conditional approval mechanism in Europe is intended for this purpose, where benefit-risk is positive, but more data are required to confirm benefit post-license.

Conversely, local regulations requiring additional studies (aiming to ensure clinical data are relevant to the local population) or having significantly longer approval times may negatively influence a country's prioritization. Increased development costs or delayed market entry to generate additional data may reduce financial returns compared to marketing a product in a country without these challenges. Ideally, a company will consider an integrated evidence generation strategy that considers evidence required by the healthcare system's multiple stakeholders and will gather such evidence in the smallest number of separate studies minimizing cost while meeting stakeholder objectives for evidence.

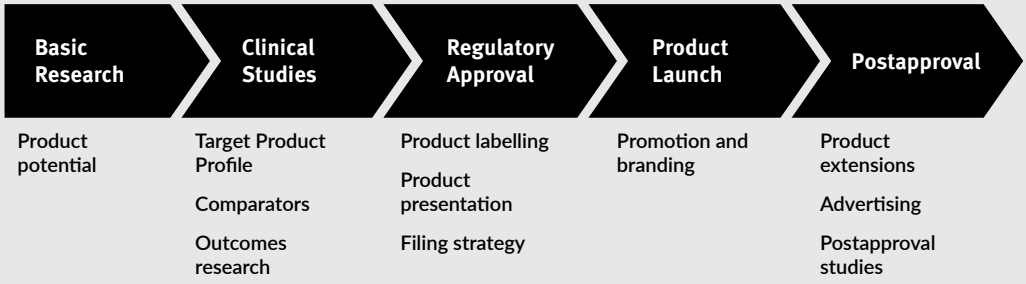
Clearly articulating claims and global market entry timing enables potential sales in key markets, development costs and return on investment to be modeled.

In early development stages, many unknowns and assumptions need to be built into the model. Scenario planning and sensitivity analysis will take these uncertainties into account, which will reduce as development progresses and challenges are overcome, creating an increasingly robust financial model to support business planning.

During development, decisions made by the multidisciplinary team will impact potential business outcomes, the financial return and subsequent patient access. Decisions should be based on data available, moving the product forward toward the overall TPP objectives. If available data indicate deviations from the planned pathway are required, a detailed TPP review and business outcome impact evaluation should follow.

The sponsor TPP and development plan are living documents and require regular monitoring and review to evaluate progress against objectives and updating as appropriate.

**Figure 15-2. Key Interactions Between Marketing and Regulatory**




### *Marketing*

During all product development stages, the marketing/commercial team contributes to the global development strategy. To present a product to its target market, three key elements must be integrated: product attributes, marketing decisions and commercialization activities. Each of these may be influenced by the regulatory strategy, label claims and product presentation.

The integrated product strategy will incorporate the overall regulatory and market strategies seamlessly. Key marketing interactions influencing regulatory strategy and vice versa are shown in **Figure 15-2**.

Each territory should contribute to and take into consideration the global product strategy when developing regulatory and marketing strategies for local markets.

Global regulatory environment changes and precedence will impact marketing strategies directly. International harmonization of regulatory requirements is increasing the opportunity for companies to file and launch new products simultaneously in multiple markets. Further, the introduction of live (adaptive) licensing, based on a medicine's early approval in a restricted setting due to positive data in the limited setting and shifting data generation in broader settings to a subsequent line extension, will impact the sales and marketing process significantly. Instead of an all-or-nothing regulatory approval approach, new medicines' approval is replaced by a cumulative process based on gradual accretion of data (the 'evidence continuum'). New therapies receive a conditional license based on further testing to substantiate their safety and efficacy in larger or different populations, thus providing early access to promising therapies, particularly for unmet needs. Over time, more data are expected to be generated in the post-license setting, and access to technology and digital health records will allow an environment that provides greater confidence to regulators and other stakeholders than has been possible before.

Marketing will be able to promote and build a new brand on an incremental basis. However, the opportunity for early market launch also carries the risk that not all products will have the anticipated benefits, as subsequent trials may show a small treatment effect or unacceptable adverse events. This risk needs to be communicated to patients and healthcare providers clearly and systems developed to monitor new medicines in the marketplace more closely. License cancellation or restriction risks and consequences should be incorporated in risk management planning.

### *Reimbursement*

While significant efforts have been directed toward global harmonization of regulatory requirements, reimbursement processes and systems are country-specific, with little or no har-

monization among jurisdictions, partly because each country's clinical, social and financial context can be so varied. However, several guiding principles underpin many health technology assessment (HTA) and reimbursement systems:

- Is the new medicine effective in the population?
- Does it have advantages over currently available therapies?
- Will it contribute to an overall healthcare savings (i.e., offset other costs)?
- Is it affordable?

The product value concept is incorporated in the sponsor TPP, with contributions from health outcomes, marketing and other integrated product development team members.

Generally, a new product's value and answers to these questions are not forthcoming from a clinical development program focused solely on achieving regulatory approval. Regulatory requirements compared with HTA authority requirements are shown in **Table 15-1**.

On its own, the data package the regulatory authority requires for marketing approval often will be insufficient to meet HTA data requirements. In countries where reimbursement is pivotal to a product's market success, data required to support reimbursement must be incorporated into the product development plan and regulatory strategy.

Late-stage clinical trial design considerations impacting HTA assessments include:

- Active comparators—is a three-way design incorporating a placebo and an active comparator feasible? How will the comparator be selected, as regional standards of care may vary?
- Are quality of life and validated instruments to evaluate patient preferences planned?
- Does the trial use broader patient populations?

Optimally, preapproval clinical trials will incorporate these data requirements. Increasingly, postapproval studies are required. These may be postapproval commitments as a condition of a live licensing program or a risk management program required by a regulatory agency. In addition, postapproval observational studies and registries provide evidence to support reimbursement submissions and continue to remove uncertainty in the postmarket setting.

## Global Product Development

### *CMC (Chemistry, Manufacturing and Controls)*

A CMC product development program focuses on the drug substance and drug product's formulation, process development and presentation as well as the manufacturing facility. From a global

**Table 15-1. Comparison of Regulatory and HTA Requirements**

| Regulators | HTA Authorities |
|---|---|
| Evaluate efficacy (therapeutic effect) | Evaluate effectiveness, how well a treatment works in the practice of medicine |
| Homogenous data | Heterogeneous data |
| Risk/benefit | Cost effectiveness |
| Comparator:<br>• placebo (FDA)<br>• active drug (EMA) | Comparator:<br>• current standard of practice |
| Focus is on the drug | Focus is on population, cost and generalizing beyond data |

perspective, the CMC development program must consider many aspects, including development phase and regional requirements.

A global CMC strategy should be integrated and linked with the overall global product strategy to ensure suitably formulated product is available to meet a particular development stage's requirements.

The three key factors influencing the CMC development program are quality, time and cost. All these factors are related, and the chosen pathway also will depend on the business's risk tolerance. For example, an organization initially may choose to save time to get the first patient for a given clinical study. However, in the end, that decision may incur higher costs and additional time or even result in a product profile that is less acceptable to patients (e.g., short storage conditions due to lack of stability data).

Initially, a non-GMP drug substance is acceptable for nonclinical studies, provided the impurity profile does not increase a toxicity risk that might not occur at later development stages when impurity limits are tighter. Frequently, only the drug substance is required for initial pharmacology and toxicology studies. However, formulation effects must be evaluated, and the drug product may be required for nonclinical studies if the product required a complex formulation due to the drug substance's physicochemical properties, e.g., low solubility, membrane permeability, stability or interactions with formulation excipients.

As the product moves into clinical studies, the CMC strategy must take clinical trial product requirements into account in countries where studies are planned. In most countries, full GMP compliance is required for all clinical study phases. However, some countries, including Australia, allow use of a non-GMP product for a first-in-human study in healthy volunteers.

The drug product presentation also must be consistent with the clinical development strategy to ensure the dosage form and dose unit meet protocol requirements. Early in development, it is recognized clinical studies may be conducted with a simple formulation, but later clinical studies should be conducted with the product planned for marketing. If significant manufacturing or formulation changes are made late in development, bridging studies may be required to confirm the changes have not altered the product's safety or efficacy profile.

Other clinical study CMC considerations include requirements for a placebo product identical in appearance to the active product for use in double-blind studies. Placebo development may be challenging if the active drug substance has characteristics difficult to emulate with an inactive substance, e.g., smell or taste.

Many countries are members of the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Cooperation Scheme (PIC/S), which provides a GMP guide for medicinal products. Annex 13 sets out requirements for clinical trial product manufacturing and labeling. This guide can assist the CMC team in planning the clinical trial product manufacturing program and core labels; however, the team always should be aware of the geographic locations in which studies will be conducted and individual country- and study-specific requirements. In some countries, e.g., India, patient labels and information are required to be in the local language, meaning up to six local languages must be accommodated. Clinical trial supply availability is a key factor in study start-up times and should be coordinated with the clinical development team. Batch records may be required for study approval, but manufacture timing should ensure, as far as possible, sufficient stability data are available to avoid the need to change batches during the study.

As the product development program moves closer to market, it is important the CMC team understands the regulatory filing strategy, desired product profile for patients and priority target countries to ensure regulatory dossier CMC sections meet both the format and content requirements for each country. International Council on Harmonisation (ICH) guidelines assist and enable manufacturers to develop a core CMC

dossier, but many individual country requirements exist for non-CTD format, stability studies across temperature zones, labeling and packaging. In addition, specific product type guidelines developed by many jurisdictions may require additional or different product specifications.

Marketing and reimbursement teams also may have country- or region-specific requirements that must be accommodated to support commercial success, e.g., a pack size equivalent to one month's supply is the maximum quantity permitted to be dispensed or reimbursed on each occasion.

### *Nonclinical*

As the nonclinical plan is developed, it must be integrated with both the clinical and CMC programs. Clinical studies must be supported by appropriate nonclinical studies. For example, nonclinical toxicology studies should use the route of administration proposed in the clinical study, of the same or longer duration. Results of nonclinical studies conducted prior to the first Phase 1 study should provide information to guide clinical study starting dose selection. Similarly, reproduction study timing generally will be determined by the timing of including women of child-bearing potential in clinical studies.

In countries that have adopted ICH guidelines, the nonclinical program required to support clinical studies generally is harmonized. However, even in ICH countries, differences exist in long-term toxicity study duration to support Phase 3 trials and marketing applications. For example, ICH M3(R2) on the duration of repeat-dose toxicity studies provides different recommendations for the EU and US. In the EU, a six-month repeat-dose study in two species (rodent and nonrodent) is required. However, the US requires a nine-month nonrodent study.

Therefore, the nonclinical plan must meet local regulatory requirements to initiate clinical studies and meet global nonclinical requirements needed to support the market application.

### *Clinical Development*

Increasingly, the clinical development program's goal should not only be global but, essentially, simultaneous.

Simultaneous global clinical development can bring many benefits to the global regulatory strategy:

- broader regulatory oversight—simultaneous submission and regulatory agency review allow the authorities' views and experiences to be included in the clinical development program
- reduced drug availability lag—successful simultaneous clinical development should result in earlier innovative drug therapy availability to populations in new markets and, ultimately, a reduction in drug lag from core countries' marketing time
- ethnic factors—broader clinical development enables a science-based approach to define intrinsic and extrinsic factors and identify meaningful ethnic differences (In addition, registration dossiers will include higher ethnic diversity.)

Global clinical development data should satisfy not only US and EU requirements, but also address ethnic differences and satisfy the local data requirements for marketing applications in countries such as Japan, China, South Korea, Taiwan, Mexico and India.

Global programs have contributed to the geographic shift in selecting countries for clinical trials. Drivers for this shift also include access to wider, often treatment-naive populations and a reduction in development costs. Increasingly, countries outside the traditional drug development core countries are offering quality sites and good investigators.

Organizations may set out to design a global clinical development program, but whether this can be truly simultaneous depends on many

factors within each country, including regulatory requirements and start-up times.

The unpredictable regulatory environment can be a major deterrent to global clinical development:

- lack of harmonized requirements and processes among countries, and unique data requirements outside international standards
- variability in acceptability of novel approaches, e.g., innovative clinical study designs
- variable and inefficient review of initial approval and amendment processes
- data acceptance and uncertain ICH GCP enforcement can raise doubts about whether trial results will be acceptable to other agencies
- intellectual property concern barriers to providing detailed information (e.g., CMC) at an early stage

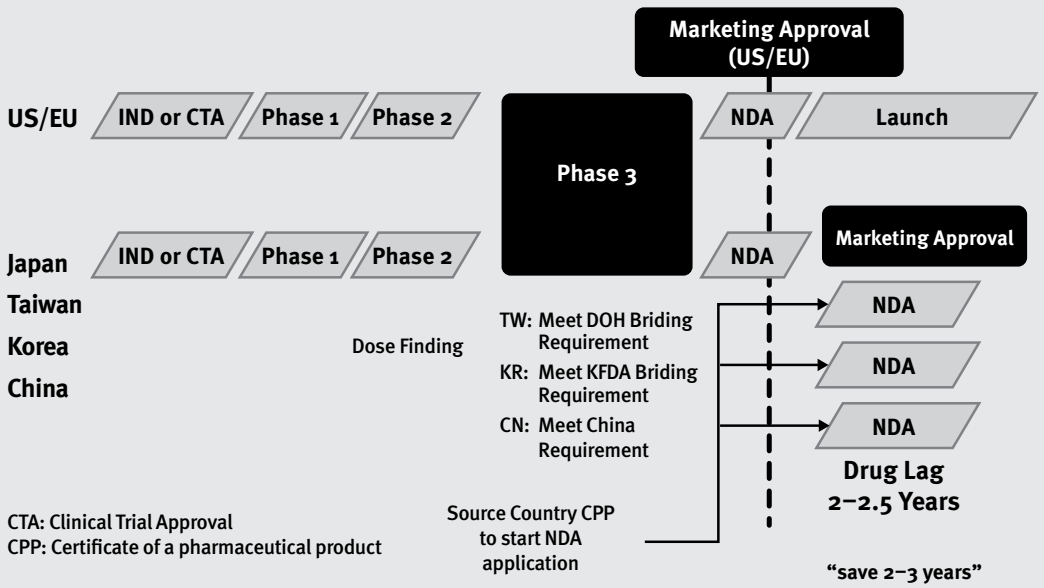
When planning a global clinical development program, prioritizing markets for commercialization and identifying the steps and regulatory requirements necessary to achieve this may influence program design significantly. For example, if in-country clinical trials are needed for regulatory approval, it may be possible to plan the clinical development program to include these countries in global trials in addition to in-country trials.

Some countries may require specific local nonclinical studies or clinical pharmacokinetic studies prior to starting later-phase studies. A global Phase 3 program may include local requirements for ethnicity or a specific percentage of patients from each region.

Failure to determine these requirements prior to starting the registration studies could result in significant cost implications and delays in marketing application submissions if they are not met.

**Figure 15-3** provides an example of the regulatory strategy to reduce approval timelines in key Asian markets by including these countries in a global clinical development program.

**Figure 15-3. Clinical Development Strategy in Asia**



Clinical study protocol design also may influence data acceptability in different jurisdictions. Regulatory guidance on developing new therapies for specific indications will influence overall study design, including objectives, endpoints, use of active comparators or placebo and study duration. In an effort to support conduct of clinical studies to meet requirements in both the EU and US, EMA and FDA provide organizations the opportunity to seek parallel Scientific Advice. The goal of parallel Scientific Advice is sharing information and perspectives, rather than necessarily resulting in harmonization of regulatory requirements. However, for innovative new products for which no specific guidance is available, agreement on development requirements may be a beneficial outcome. Increasingly, it also is desirable to obtain advice in parallel with reimbursement authorities to drive alignment in what the regulatory authority and subsequent reimbursement authorities would prefer to see in the overall evidence package.

## Dossier

### *Core Dossier*

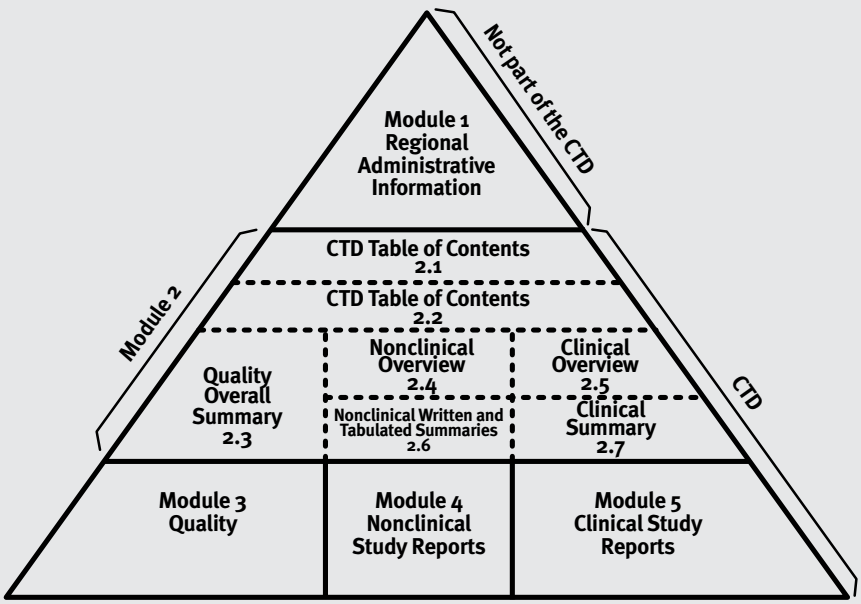
Regulatory agencies expect an assurance of medicines' quality, safety and efficacy before they authorize their distribution to patients in their countries.

While the information required by each country's regulators differs, ICH has developed some harmonization of standards among countries. In addition to the three ICH regions (US, Europe and Japan), many countries have adopted ICH guidelines, including Australia, Switzerland and Canada.

ICH has developed a standard content format, the Common Technical Document (CTD), that also is organized with consistent sections and headings[2] (see **Figure 15-4**).

Module 1 is for administrative information and prescribing information and should contain region-specific documents, e.g., application forms or the proposed regional label. Module 1 is outside the formal ICH guidelines, and each

**Figure 15-4. The CTD Triangle**



jurisdiction that has adopted ICH guidelines also has developed specific Module 1 guidance.

ICH publishes structure and content guidelines for Modules 2–5.

Module 2 contains summaries of the organization's position on available data and summaries of quality (QOS), safety (CSS, NCO) and efficacy (CSE, CO). Regulators require the sponsor to provide its assessment of the product's overall benefit-risk balance in this section, including any outstanding uncertainty in either risk or benefit at the time of initial regulatory review.

Module 3 provides information related to how the product was developed, how it is manufactured, evidence of product stability under standard and stressed storage conditions and data ensuring it can be manufactured reproducibly and analyzed to generate a reproducible product meeting an appropriate release specification.

Module 4 provides information related to completed nonclinical analyses.

Module 5 provides the sponsor's clinical trial study reports demonstrating a tolerable safety profile and positive beneficial effect.

ICH also has authored guidelines (quality, safety and efficacy) clarifying expectations for the information these sections should contain.

For a global organization, the goal is to generate a core regulatory dossier efficiently that can be reused in multiple markets where it may wish to register the product. Generating this dossier, therefore, may take some regional differences and requirements across markets into account. For example, the core quality section may describe process information related to a range of manufacturing facilities supplying several markets, allowing this information to be selected for the relevant local dossier.

A regulatory professional has multiple roles in generating the regulatory dossier:

- advising on content requirements
- ensuring coordinated delivery of multiple components
- ensuring a balanced benefit-risk assessment that acknowledges product weaknesses and uncertainty, allowing regulatory reviewers to focus on the product's key outstanding issues
- ensuring the messages delivered are simple, clear and succinct to aid the agency's regulatory review and decrease agency questions

Organizations generate the filing documents required to complete each CTD section, but following initial approval, may need to modify specific sections using a variation, amendment or supplement. For example, additional clinical data may be generated with the intent of expanding the product's use, and the sponsor will be required to provide a new clinical study report (CSR) and proposed label changes to support the new use.

Companies often initially generate an ICH-style dossier first and use this to generate the dossiers for non-ICH countries.

### *Regional Dossiers*

The dossier's content and structure may need to be modified to meet each regulatory authority's requirements in the region or country in which the organization wishes to register the product. This may include a range of additional considerations. Some examples are provided below, and specific requirements are called out at a high level in **Table 15-2**.

- Providing extra data—some regulatory agencies require additional clinical data representing the local population, e.g., China, Japan, etc., or data with an alternative comparator representing that market's standard of care.
- Additional declarations—legal letters of authority, Certificates of Analysis, executed batch manufacturing records all are examples of country-specific additions.
- Local forms—application forms, local language versions of clinical summaries, Certificates of Pharmaceutical Product (CPPs) confirming prior approval in another jurisdiction (typically US or EU).

**Table 15-2. Overview of Specific Country Requirements**

| Country | Global Dossier | Local Trials | Local Language | CPP Required | Specific Requirement |
|---|---|---|---|---|---|
| US | ICH CTD | Representative ethnic mix | English | No | Patient-level data Integrated<br><br>Summary of Safety and Efficacy |
| EU | ICH CTD | Representative ethnic mix | English, plus local language required for product information | No | |
| Japan | ICH CTD | Required | Japanese | No | |
| Australia | ICH CTD | Generally No, except bioequivalence studies using local product as comparator | English | No | Australian-specific Risk Management Plan |
| China | Local format | Required | Chinese (Mandarin) | Yes | Extensive dossier required for clinical trial approval |
| South America | Mixed—ICH CTD and local format | Mixed—some countries require local data, some do not | English, plus local language required for product information | Mixed | |

- Alternate formats—some regions, like the Association of Southeast Asian Nations (ASEAN) require their own dossier format (e.g., the ASEAN CTD). This format incorporates both summaries and detailed reports into one part, e.g., Part IV includes both the clinical summary and clinical study reports. Formatting at a practical level can be as specific as the color of the tabs between sections or page numbering, and care must be taken to meet these formatting requirements for countries retaining these specific dossier validation needs.

An alternative commercial strategy may require tailoring the dossier, e.g., where different data are required to register attributes for a specific market.

- Quality differences—registering alternative presentations, manufacturing sites or supply routes in a specific country, different release specifications or humidity and temperature conditions requiring alternative storage or stability data.
- Clinical differences—intention to register an alternative indication or additional local data. This data inclusion may require a new clinical review or modification of other sections, e.g., integrating new data into safety summaries and summary tables. Some markets also may require clinical data comparing the product to that market's current standard of care.
- Timing difference—depending on when the original filing is submitted, a current dossier version incorporating the sequence of changes that have occurred may be required. For this purpose, good practice is to keep a 'current master version' in addition to tracking versions and content registered in each market.

### *Planning Filing Sequence Across Global Markets*

The dossier generation and filing sequence planning strategy is the regulatory professional's

responsibility, in consultation with the global multidisciplinary development team. Some markets do not accept applications until one of the ICH (i.e., reference) countries completes its review. Once this initial review is complete, a CPP can be issued confirming a satisfactory review was completed in another jurisdiction. This can mean other markets can do a slightly abbreviated review based on the fact the prior review has occurred, known as a reliance mechanism. This allows regulatory submission to take place in waves.

Key considerations when planning a filing timeline include:

- availability of required filing data, e.g., local market data
- prior reviews, e.g., in an ICH country (US, EU, Japan) (including an ability to leverage responses to these questions elsewhere)
- launch time commercial driver (impacted by market dynamics), e.g., when does the organization want to initiate distribution, as soon as possible or at a defined time
- resource availability to complete the filing (including responding to agency questions)
- desired filing sequence (knowing agencies discuss reviews with each other, and agreement on specific label language in one region can impact the review outcome in another)

## Lifecycle Management

### *Postapproval Commitments*

At the time of initial registration, a company will have limited experience and exposure with its drug and some uncertainty. In the past, regulatory approval was 'all or nothing.' When a product is approved for marketing, a regulatory agency has relied almost exclusively on spontaneous adverse reporting programs to monitor a new product's safety in the marketplace.

More recently, an increasing number of jurisdictions require Risk Management Plans (RMPs) to be submitted as part of marketing applications and require formal postapproval activities to ensure appropriate prescribing and usage and to monitor and manage product safety. Although detailed RMP guidelines and formats vary across jurisdictions, the risk management principles articulated in the International Standard ISO 31000 generally apply.[3]

From early planning and as product development progresses, ISO 31000's principles can be applied to enable early product risk identification and assessment, together with mitigation plans to minimize these risks during further development, at product launch and postapproval.

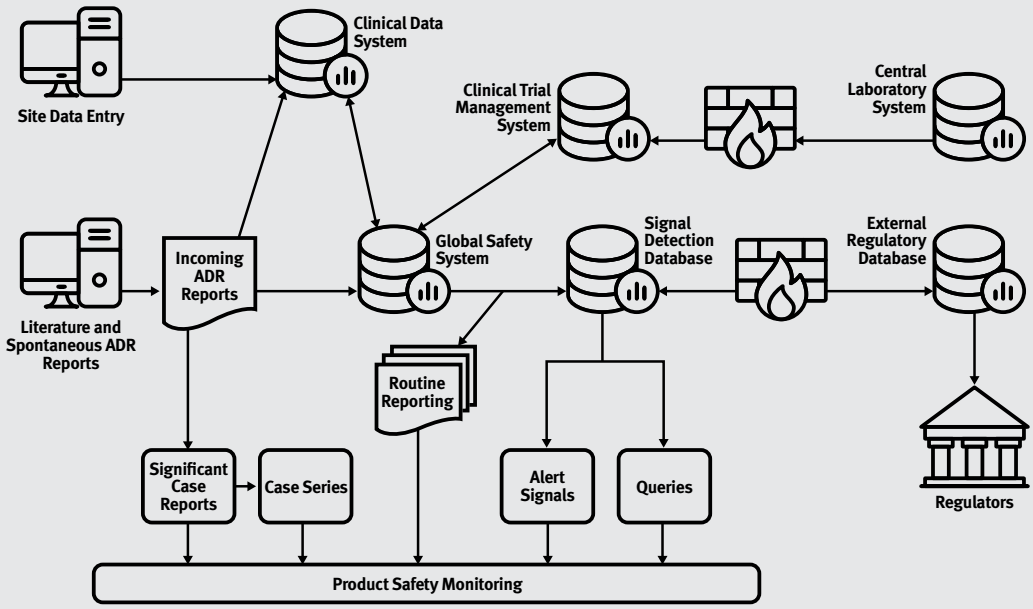
When planning and preparing marketing applications for each jurisdiction, the residual risks and management strategies identified in a global RMP can be customized to produce jurisdiction-specific RMPs.

During the evaluation process, the regulatory agency may identify new risks or request alternate management strategies. These may be country-specific issues, such as those associated with prescribing patterns or healthcare practices. In these instances, country-specific responses are required. Alternatively, these may potentially be issues relevant around the globe. Coordinating global risk management planning and incorporating these issues into RMPs and postapproval activities provide the opportunity to maintain a globally harmonized lifecycle maintenance approach. Issues initially restricted to one country or jurisdiction may, in time, be applicable to other countries, and the understanding and knowledge gained then can be shared for mutual benefit.

The need to globally coordinate postapproval commitments will increase as adaptive licenses are granted. Adaptive licenses acknowledge data continue to accumulate after a license is granted, and access is best addressed by repeat cycles of learning and confirming (re-licensing) over the product lifecycle continuum.

Increased monitoring of real-world performance (Real World Evidence, RWE), including postauthorization efficacy and safety studies

**Figure 15-5. Global Technology System for Safety Monitoring**




and registries, will be required. This is especially true when smaller data packages were initially relied upon to gain regulatory approval and this evidence may be required by other stakeholders such as reimbursement authorities. For countries with relatively small populations, global cooperation among regulatory agencies and global studies are required to provide the breadth and depth of additional data required to support ongoing approval. Overall, this lifecycle management approach is expected to lead to lower patient risks compared to the current approach, despite smaller early data packages.[4]

The International Coalition of Medicines Regulatory Authorities (ICMRA), formed in December 2013, provides a forum for developing a cooperative approach among regulators on many topics, including postapproval commitments. This group and other such coalitions of authorities in multiple jurisdictions can utilize reliance mechanisms, working together to share reviews, guidelines and best practices, and can be useful tools when considering filing strategies.

### *Safety Monitoring*

Clinical product development risk assessment must be thorough and rigorous. However, it is impossible to identify all safety concerns during controlled clinical trials. Once a product is marketed, the number of patients exposed generally increases dramatically, including those with co-morbid conditions and/or taking concomitant medications. Therefore, postmarketing safety data collection and clinical risk assessment are critical for evaluating and characterizing a product's risk profile and making informed risk minimization decisions. The growing trend for early approvals based on less-extensive clinical trial data further increases this imperative.

Postmarket safety data monitoring now is a universal regulatory authority requirement for marketing approval and may include formal postapproval clinical studies, monitored release programs and spontaneous reporting programs.

Although these postapproval obligations are mandated by agencies at the jurisdiction level,

reporting requirements are predicated on both local and global monitoring programs.

Safety scientists, therefore, must find ways to capture, record and analyze huge amounts of safety information across different studies, systems and jurisdictions and coordinate this information globally to meet reporting requirements, make informed recommendations and implement decisions.

Global pharmacovigilance processes and workflow are supported most effectively by using a global pharmacovigilance system as a technology tool for drug safety detections, data mining, results interpretation and decision-making support. Such systems are transforming industry's capability to detect safety signals early as a key component of meeting regulatory authorities' postapproval requirements and demonstrating a commitment to safety that transcends regulatory compliance.

An example of a global technology system supporting improved safety monitoring is shown in **Figure 15-5**.[5]

It is important to acknowledge a global technology system is a support tool and must be used within the global policy and procedure framework to establish a culture of safety and quality and provide the expertise and resources at both the global and local level.

Globally, these will include:

- establishing functional groups and expertise
- developing and aligning integrated operational procedures
- developing and implementing well-defined decision-making models, escalation processes and communication channels
- incorporating continuous improvement activities

These principles apply regardless of the organization's size, the number of products or number of jurisdictions. Newly launched products generally are the focus of key postapproval monitoring. There are notable examples of products withdrawn from the market many years after initial launch due to long-term safety studies initiated after a series of spontaneous reports alerted regulators to potential concerns.

Opportunities exist for greater international collaboration among regulators who potentially have access to bigger pharmacovigilance datasets and data mining capabilities, as well as increased collaboration and harmonization on regulatory decisions. The next wave in this workflow is the introduction of artificial intelligence to enhance data mining and uncover new insights from large data sets.

### *Maintenance and Compliance*

Throughout the lifecycle, product registration must be maintained in accordance with regulations in each jurisdiction in which it is approved. Variations to the current approved product may require a submission and regulatory authority approval, depending on the nature of the proposed change. Similarly, the approval timelines, and such provisions as grace periods (for implementation), vary widely in different regions.

Whenever proposed changes are planned, e.g., a quality change such as a packaging change, they ideally should be planned well in advance of implementation. A global plan is required, including an understanding of region-specific requirements for the proposed variation, e.g., data requirements, submission format, timelines and costs. It is good practice to assess the change's intended impact and benefit, e.g., a minor change in manufacturing may take more time and effort to introduce than the savings in efficiency intended locally in the plant.

Similarly, changes relating to new clinical data availability to extend the approved indications may be planned well ahead of time at both the global and local levels.

As with new product submissions, a sponsor may elect to compile a core global variation dossier, accessible via a central database, with local requirements added at a regional or country level. The submission then is managed at the

local level, with local regulatory staff responsible for regulatory agency interactions.

Other changes, such as safety-related updates following unexpected serious adverse events and signals detected through postmarketing surveillance, often are accompanied by tight regulatory timelines for notifying the regulatory agency and updating product information documentation to ensure new risks are communicated promptly to patients and healthcare professionals. Although it is not possible to plan specific regulatory interactions in advance, global planning for such events is vital to enable rapid implementation if these occur. A multidisciplinary team including experts in regulatory and safety, compliance, risk management, communications and marketing should document procedures and ensure all key staff (and backups) are trained and ready to implement the plan, if necessary. A local plan should be developed, consistent with each region and country, that links into the global plan.

## Knowledge Management

Knowledge management is one of the most significant regulatory challenges. Regulatory expertise often is comprised of knowledge of what is written in regulation, knowledge of precedence and actual personal experience and a set of relationships with the relevant authority that help the regulatory professional collectively provide advice on what is 'required' and what is 'expected' to deliver a positive outcome.

### *Experience Capture*

Properly captured knowledge and centralized information sources yield process efficiencies. Actions taken by companies for proper knowledge codification and dissemination include:

- creating an "expert tracker" database for knowledge residing with the organization's employees and attempting to centralize and disseminate that information
- disseminating information through multi-level training at different career stages for regulatory and affiliated personnel
- creating customized reports interpreting regulations and ensuring the regulatory function is the ultimate authority on all regulatory compliance aspects
- tracking regulatory key performance indicators with a balance of lagging indicators (e.g., issues generated after product launch) and leading indicators (e.g., revenue at risk from potential regulation changes)

Regulatory functions within organizations, especially those with global programs, should not be merely reactive and tactical, but more proactive and aligned with the organization's global product strategy to ensure minimal regulatory compliance challenges and timely mitigation of nonconformance risks.

### *Regulation Database*

Companies need to have reliable, current knowledge databases to track technical and legal requirements for each country in which they intend to submit regulatory dossiers. Commercial databases are available, and/or companies can utilize staff to provide local intelligence. Local direct intelligence advantages include supplementing local published guidance with practical insights and experience of what actually was required in addition to what was published. If using a commercial database, the information's currency should be confirmed, as regulations change frequently, especially in countries with evolving regulatory frameworks.

### *Knowing the Regulatory Authority*

Organizations need to know not only the written regulatory requirements, they also should have a good understanding of unwritten requirements and the personal preferences of any agency reviewers who may review their dossiers.

If possible, regulatory personnel should be encouraged or advised to interact with the regulators during new product development, although it is not possible or efficient to meet with all

agencies. These interactions can help the organization get to know the future agency review team, help that team become familiar with the product's innovative aspects and gain input on the proposed strategy.

All regulatory agencies expect companies to be truthful, transparent, collaborative, science-based and patient-focused in all interactions.

### *Language, Culture and Local Insights*

To be successful, it is important companies understand which documents must be presented in the local language. This might include packaging, patient or physician leaflets, clinical summaries, etc.

Holding meetings in the local language can show respect for the culture, especially where facilitated by a representative from the country who is aware and respectful of specific expectations. For global companies, this step can be cumbersome.

Local language negotiations or discussion of highly scientific dossier review aspects also may be more fruitful in the local language if the reviewers are less comfortable with an alternative language.

Some countries have specific format requirements, which may extend to electronic format, paper color for the printed dossier, signatures and required dossier page numbering, etc. Insights into each of these requirements will ensure speedy validation and subsequent dossier review.

### *Regulatory Authority Meetings*

Global organizations may plan to interact with specific regulatory agencies to gain feedback on available data and intended next development process steps. In general, companies will interact with only a limited number of regulators to get a sense of their intended action's likely acceptability. Companies intending to market in the US normally will interact with FDA at defined milestones; similarly, if intending to market elsewhere, key interactions may include meetings with EMA (and/or specific national European regulatory authorities), Japan's Ministry of Health, Labour and Welfare, Health Canada, Australia's Therapeutic Goods Administration or others. Key agency meeting considerations may include:

- data reporting impacting benefit-risk conclusion and requiring review before advancing to the next phase
- clinical design issues requiring discussion (e.g., where there is an intention not to follow regional guidance and expectations or where a specific innovation is intended in the trial design)
- defining milestone meetings, e.g., End-of-Phase 2 (EoP2)
- technical reviews with specific committees, e.g., biotechnology products or advanced therapies
- preapproval reviews, e.g., Advisory Committee Meeting
- presubmission interactions to familiarize the review team with the dossier and allow in-person discussion and clarification ahead of dossier submission

The global product strategy team's job is to define the overall corporate product development strategy, assimilate the feedback from multiple jurisdictions (and possible stakeholders if joint HTA advice is also sought) and propose a plan that takes feedback obtained into account. It is good practice to document the advice received and capture why the company chose not to follow that advice, as this is likely to come up during the subsequent marketing authorization application review.

### *Electronic Submissions*

To facilitate submission, navigation and review, many countries accept electronic dossiers. To ensure presentation is in a common format, ICH has agreed on a common format known as the electronic Common Technical Document (eCTD).[6] The table of contents is consistent with the CTD, and the document is structured in HTML format. Since this field is evolving, current standards should be verified via ICH or country-specific websites prior to dossier com-

pilation and submission. For example, since July 2015, eCTD submissions have been mandatory for all EMA centralized applications.

Many countries do not accept eCTD yet, but may accept a non-eCTD electronic submission (NEES). NEES differs from an eCTD because it does not have an XML backbone or MD5 checksum, as defined by ICH. Rather, it is a collection of electronic files organized in folders.

## International Cooperation and Harmonization

As organizations seek to increase their drug development programs' efficiency by increasing their focus on early and simultaneous registration in multiple global markets, regulators also are growing more aware of the need for global harmonization of requirements and processes. Efforts to increase global harmonization are continuing through a range of activities in addition to ongoing ICH processes.

### *ICMRA*

ICMRA provides direction for a range of areas common to many regulatory authorities' missions. It identifies areas for potential synergies among regulators and facilitates, where possible, international leveraging and resource savings by building confidence and deeper regulator collaboration.

### *International Generic Drug Regulators Programme (IGDRP)*

IGDRP was created to promote collaboration and convergence in generic drug regulatory programs for regulatory agencies from several countries.

### *International Regulators Consortium*

This consortium was formed in 2007 by like-minded regulatory authorities to promote greater regulatory collaboration and alignment of regulatory requirements.

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